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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GUPTA, ANISH

ART UNIT	PAPER NUMBER
1654	8

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,070	Applicant(s) VISSER ET AL.	
	Examiner Anish Gupta	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The preliminary amendment filed 5-31-01 has been entered. Applicants requested the entry of page 1 and 1A for page 1 of the specification. Applicants also requested cancellation of claim 12, addition of claims 13-14 and amendment to claims 3-11. Claims 1-11 and 13-14 are pending in this application.

Specification

2. The disclosure is objected to because of the following informalities:

The MPEP, under 37 CFR 1.821(d), requires that "reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims. . ." On pages 15- 18 of the specification, the sequences recited do not contain sequence identifiers.

Appropriate correction is required.

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

4. Claim 11 is objected to because of the following informalities:

The MPEP, under 37 CFR 1.821(d), requires that "reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims. . ." Here, the claim recites sequences without the required sequence identifier.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-11 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the process claimed is not a process of production but a process of purification. The method steps listed in the claim all purification steps that isolate the desired peptide rather than produce the peptides. The claim does not recite any steps, i.e. recombinant and or synthetic steps, that would "produce" the peptide. Applicants are requested to amend the claim to recite a process of purification rather than process of production to better characterize the claim.

In claim 10, culture cells and plant cells are not considered to be a "biological fluid(s)." Cells are solid masses that contain biological fluid, but are not biological fluids themselves.

In claim 11, the claim recites "an amino acid sequence selected from the following sequences (1)-(8)..." However, it is unclear if (1)-(8) refers to the peptides listed at the end of the claim or some other peptides. Applicants are requested to list the sequences after the phrase "an amino acid sequence selected from the following sequences" to avoid any confusion.

In claim 11, the claim states "derivatives thereof having a primary amide at the carboxy end thereof. . .". However, it is unclear as to the precise definition of a derivative. That is, does the derivative always consist of a primary amide or does the derivative include other modifications in

amino acid sequence. In essence, the claim does not specifically state what modification are necessary in the amino acid sequence to render it a derivative.

In claim 11, for the sequence PEWSKCYQWQRRMRKLGAPSITICIRRTSA, it is unclear what amino acids are involved in the disulfide linkage. The "*" is embedded between two amino acids in two different locations, implying that a disulfide linkage could exists between two of the four amino acids. Applicants are requested to specifically identify the amino acids involved in the disulfide bridge.

Written Description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11, 13-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus,

> an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the

genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a derivatives of the peptides claimed in claim 11. The claim states that the derivative has a primary amide at the carobxy end and do not interfere with any biological properties. This generic statement for the derivative peptide fails to adequately describe a structural feature common to the genus since the only common feature would be an amide bond between the amino acids. Further, the polypeptide and proteins of the claims are not limited to any specific class of compounds for which one could readily obtain physical and/or chemical properties or functional characteristics thereby obtaining some insight as to the structure of the desired proteins or polypeptide. The specification does not provide a single example of what qualify as derivatives of the claimed peptides. The specification, as a whole, does not sufficiently provide ample definition, such as by structure, formula, or chemical name, of the claimed subject matter sufficient to distinguish it from other peptides. Accordingly, the disclosure lacks sufficient written description to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 11 is a broad generic with respect to derivatives. The possible structural variations are limitless, especially in the light of a lack of teachings for derivatives in the specification, since any side chain maybe modified, any amino acid may be deleted and/or any amino acid maybe substituted. The number is not limited by the limitation of "biological properties", since the peptide can have any biological activity. Thus, so long as a peptide has some biological activity, relative to the native, for any biological process, the peptide qualifies as a derivative. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the sequence. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of any peptides that contain structurally distinct substitutions that could be used as a benchmark for the definition of derivatives. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.").

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) Nature of the Invention

The invention is drawn to process of purifying peptides form biological fluids, wherein the peptides are hydrolyzed while adsorbed onto a chromatographic medium. The invention is also related to the methods of using these isolated peptides.

(2) The State of the Prior art

It is well known in the art that anti-tumor drugs such as anti-angiogenic drugs, while effective in vitro and in mice, are not effective in humans. For example, Dermer states that "immunotherapy's killing power of the transformation of 3T3 cells by a mutated protooncogene, simply does not have the same significance for cells in vivo.' (See page 320). Further, "[t]he facts indicate, however, that petri dish cancer is really poor representation of malignancy, with characteristics profoundly different from human disease." (See page 320). Similar sentiments are echoed in a Science article by Trisha Gura. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide n culture." (See page 1042). In essence, the art indicates that "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than cancer or diseases of the central nervous system." (See Time article by Frederic Golden on page 44).

The art has also recognized some peptides that have been claimed in this invention. The art indicates that the peptides are useful in inhibiting blood platelet aggregation and are useful for the treatment of thrombosis (see Kizawa JP03255095, CaPlus abstract). However, the prior art does not teach the effectiveness of these peptides against tumors or for the treatment of antimicrobial or viral infections.

(3) The relative skill of those in the art

The relative skill of those in the art his high.

(4) The predictability or unpredictability of the art

When dealing with any biological treatment methodology wherein the end result is ameliorate some biological condition, the unpredictability is very low. This is especially true when the art does not teach the disclosed method of treatment. In this case, the predictability of the peptides treating microbial, viral infections, or treating tumors is very low since the art does disclose the ability of peptides claimed to have such activity.

(5) The breadth of the claims

The claims are drawn to method of treating microbial or viral infections in warm-blooded animals or treating tumors by administering an "effective amount" of the peptides of the sequence claimed in claim 11 or derivatives thereof.

(6) The amount of direction or guidance presented

The specification does not provide ample guidance for one of ordinary skill in the art to treat microbial or viral infections and/or treating tumors. One of the most glaring omissions in the specification is the complete lack of guidance with regards to dosage and modes of administration to obtain the desired end result. The MPEP states that "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or

method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph." However, the specification does not indicate any similar compounds that one of ordinary skill in the art could readily ascertain the desired dosage. The specification is entirely void of any guidance from which one could ascertain the "effective amount" necessary to practice the claimed invention. This is also true of the mode of administration necessary to use the claim invention. The specification does not recite which pharmaceutical carriers could be used or which pharmaceutical formulation can be used. It should be noted that certain peptides are free of the prior art and as such no guidance is available from the prior art at large for pharmaceutical formulations. Thus, the specification lacks proper guidance into the dosage and modes of administration to allow one of ordinary skill in the art "to use" the claimed invention.

With respect to treatment of tumors, the specification is void of guidance as to how the tumors are to be treated and which tumors will be treated. It is known in the art that there are two general types of tumors, solid tumors that require the development of a blood supply to metastasize and enlarge, and soft tumors that may have circulating cells, as in leukemia. The pathologies of these tumors are different and as such treatment methods for one do not correlate to treatment methods for the other. "For example, the soft tissue tumors (e.g., lymphomas), and tumors of the blood and blood-forming organs (e.g., leukemias) have generally been more responsive to chemotherapeutic therapy than have solid tumors such as carcinomas. One reason for this is the greater physical accessibility of lymphoma and leukemic cells to chemotherapeutic intervention. Simply put, it is much more difficult for most chemotherapeutic agents to reach all of the cells of a solid tumor mass than it is the soft tumors and blood-based tumors, and therefore much more difficult to achieve a total cell kill. The toxicities associated with most conventional antitumor agents

then become a limiting factor" See Thorpe et al. (US 5776427). It is clear, then, that one could not treat any type of tumor with the claimed peptides. With that said, without ample guidance as to the effectiveness of the peptides to specific types of tumors one would be burdened with undue experimentation to determine the types of tumors that could be potentially treated by the peptides.

(7) The presence or absence of working examples

The working examples do not remedy the deficiencies of lack of guidance in the disclosure since the specification does not disclose any working examples. It is acknowledged that the specification provides examples on how to make the peptides and assays for antibacterial activity, but the specification does not provide any models by which in-vivo therapy information could be ascertained. For example, the lack of animal models prevents one of ordinary skill in the art to obtain the proper dosage regiment. From the assay methods alone, one cannot extrapolate the required dosage necessary to treat antimicrobial infection with "effective" amount of the peptide.

For tumor treatment, no working examples are present including in-vitro methodology. Although working examples are not required, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Here, the state of the art has indicated cancer therapy, even with animal models, is not entirely predictive of clinical efficacy. As stated above, Dermer states that "immunotherapy's killing power of the transformation of 3T3 cells by a mutated protooncogene, simply does not have the same significance for cells in vivo.' (See page

320). Further, "[t]he facts indicate, however, that petri dish cancer is really poor representation of malignancy, with characteristics profoundly different from human disease." (See page 320). Similar sentiments are echoed in a Science article by Trisha Gura. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041). Given the problems associated with animal models, one could not readily ascertain the effects on animals without **any** working examples.

(8) The quantity of experimentation necessary

The Board of Appeals has held *Ex parte Sudilovsky*, where it was held that the disclosure was non-enabling since:

> "[t]he specification, though highly detailed, is devoted solely to a description of compounds stated to be known ACE inhibitors. The remainder of the specification is directed to how to make tablets and solutions for injection. Any disclosure regarding utility is confined to broad allegations and suggestions without substantiating working example. As stated in *In re Glass*, 492 F.2d 1228, 181 USPQ 31, 35 (CCPA 1974), 'the strong feeling one gets from reading the entire specification is that either appellant did not have possession of the details of a single operative process or, if he did, he chose not to divulge them.'"

Ex parte Sudilovsky, 21 U.S.P.Q2d 1702 (BPAI 1991). Similarly, the disclosure of the instant application, with regard to the treatment of microbial or viral infections and treatment of tumors, is confined to broad allegations and suggestions without substantiating working examples. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to

substantiate them. In re Novak, 306 F.2d 924, 134 USPQ 335 (CCPA 1962) 4; In re Fouche, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). In this case, the disclosure has not provided evidence of record of a single compound that is effective in the treatment of viral or microbial infections or the treatment of tumors. Thus, given the unpredictability o f the art, the amount of guidance given with regard to dosage and the types of tumors to be treated, and the lack of working examples, undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Kizawa et al. (Chemical abstract No 1996:675428).

The claims are drawn to peptides of the sequence VYQHQKAMKPWIQPKTKVIPYVRY and VYQHQKAMKPWIQPKTKVIPYVRYL.

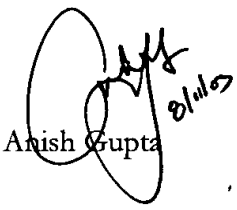
The reference discloses peptides of the sequence VYQHQKAMKPWIQPKTKVIPYVRY and VYQHQKAMKPWIQPKTKVIPYVRYL (see abstract). These peptides disclosed are the same peptides as claimed in claim 11 corresponding to peptide (3) and peptide (4). Although the reference does not teach a similar process of purification, claim 11 is a product by process claim. The MPEP states, citing In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), "[E]ven though product-by-process claims are limited by and defined by the process, determination

of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable." Here the product disclosed in the prior art is the same as the claimed invention and therefore the claim is anticipated.

11. Claims 1-10 are free of the prior art. The claims are drawn to a method of purification wherein hydrolysis of the peptide is conducted in-situ on a choromatographic medium. The closest prior arts Smith et al. (WO97/16460) does not teach in-situ digest of the polypeptides on a chromatographic medium and Azuma (JP48010543) does not teach the adsorption of the protein onto the chromatographic medium prior to in-situ digestion. There prior art does not fairly teach nor suggest the the method claimed in claim 1-10.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Anish Gupta